Remarks

Claims 35-43 and 48-52 are canceled. Claim 53 is added. Therefore, claims 44-47 and 53 are pending. In response to the Examiner's remarks, claims 44-45 are amended to more clearly define the metes and bounds of the invention by clarifying that the transgenic mouse comprising human heavy and/or light chain variable region loci replacing mouse endogenous heavy and light chain immunoglobulin variable region gene loci. Support for this amendment is found throughout the specification, including, for example, at page 10, line 29 to page 11, line18, p. 43, lines 1 and 10-15. Claim 47 has been amended for better conformity with the claims it depends from, and the alternative element (b) is now specified in a new claim 53. No new matter is added by the amendment, and the examiner is respectfully requested to enter them.

I. Formal Objections

A. The priority claims as submitted in the preliminary amendment was requested to be updated to include the patent number of the allowed parent application. Accordingly, the specification is amended above to update the information.

B. The disclosure was objected to for containing an embedded hyperlink. Accordingly, the specification is corrected to remove the hyperlinks.

C. Claim 52 was objected to for being in improper form. The objection is moot as claim 52 is cancelled.

II. Rejections Under 35 USC § 112, first paragraph.

Claims 35-39 and 44-47 were rejected for lack of enablement. Claims 35-39 are canceled. This rejection is traversed as it may be applied to the amended claims.

Claims 35-39 have been cancelled mooting the Examiner's comments regarding ES technology being limited to mice. This rejection does not apply to claims 44-47 as they are limited to a transgenic mouse. It is noted that claim 46 is amended to depend on claim 44 or 45, and the process steps removed. Accordingly, in light of the above amendments, it is believed that this rejection may be withdrawn.

III. Rejections Under 35 USC § 112, second paragraph.

Claims 44-47 were rejected as indefinite on the basis that the term "operably linked" implies that transcriptional activity of the gene loci is linked. Claim 46 was held to be indefinite

because it embraces a transgenic mouse containing an endogenous gene locus that has been replaced with an exogenous gene locus, and thus would no longer contain the endogenous locus. Although applicants do not agree that the term "operably" is conventionally used with the limited meaning proposed by the Examiner, the claims have been amended to remove the term "operably" and further define linkage as meaning that a variable region locus is joined to a constant region to form a hybrid locus that can rearrange during B-cell development. The claims have also been amended to clarify that the endogenous locus has been replaced with the corresponding human gene locus. It is believed that this rejection may now be withdrawn.

IV. Rejections Under 35 USC § 102(e).

Claims 35-39 and 44-47 were rejected as anticipated by Jakobovits et al. (US 6,130,364). Claims 35-39 are cancelled. Applicants respectfully traverse this rejection as it may be applied to amended claims 44-47.

Jakobovits et al. discuss a method for modifying the DNA encoding an antibody in an antibody-producing cell. Modification of the constant region is proposed to be useful for changing the isotype or introducing a gene encoding another molecule such as an enzyme (col. 9, lines 15, 27). Modification of the variable region is proposed to be useful for changing the specificity or affinity of the antibody encoded by the cell (col. 9, lines 27-35). The modifications are made by a two-stage process. First, a lox site is introduced into an antibody-producing cell (col. 15, lines 54-64). Then the modifying sequence is introduced by site-specific recombination at the previously introduced lox site(col. 17, lines 43-54). Most of the specification is directed to methods in which both the initial introduction of a lox site and the subsequent modification by recombination at that site are performed on hybridoma cells. However, in one embodiment discussed at col. 15, lines 27-52 and in the claims, the lox site is not introduced into a hybridoma but into an ES cell to form a transgenic mouse. Hybridomas produced by such transgenic mice already have a lox site at the appropriate genomic location. Thus, antibodies produced by such hybridomas can be modified by recombination at that site.

The present claims are distinguished from the cited patent in numerous respects. First, the transgenic mice discussed in the patent are relevant only as a means for generating hybridomas that will provide the subject for antibody modification. By contrast, in the present claims, the transgenic mice themselves are modified to produce chimeric antibodies. Second, the modifications performed in the cited patent on hybridomas are of the rearranged genes encoded by the hybridomas. Such is apparent from the purposes described for modifying

variable region (i.e., changing specificity or affinity). Antibody genes do not encode an antibody having any specificity or affinity until they have undergone rearrangement. By contrast, the present claims specify hybrid loci that rearrange during B-cell development. Third, the nature of modification proposed in the patent is different than that specified in the present claims. The patent proposes changing the affinity or specificity of variable regions not replacing a mouse variable region with a locus, and particularly not such that the human locus is thereby linked to a mouse constant region locus.

The specific sections of the patent referred to by the Examiner will be briefly addressed in turn. Col. 6, lines 34-49 discussing modifying the variable or constant regions of an antibody. However, this excerpt does not say that the modification occurs in a mouse or identify the nature of the modification (e.g., human variable region locus replacing mouse variable region locus). As discussed above, the modification in fact occurs in an antibody-producing cell. Col. 7, lines 36-55 discusses transgenic mice containing a lox site. These mice are the product of the method described at col. 15, lines 24-52, in which a lox site is inserted into transgenic mice with human genomes, such as those in the cited Kucherlapati reference. These mice have randomly inserted human immunoglobulin genes. These mice are used to generate hybridomas, which are the subject of a subsequent modification step. There is nothing in col. 7 to indicate that these mice themselves have human variable region loci replacing endogenous mouse variable region loci, as claimed. Col. 8, lines 17-65 is simply a discussion of immunoglobulin gene structure, and provides no indication to produce transgenic mice as claimed. Col. 9, lines 13-15 refers to introducing modifying sequences into antibody-producing or embryonic stem cells. However, as col. 15, lines 27-52 makes clear, the contemplated modification of ES cells is the introduction of a lox site. Finally, col. 10, lines 3-6 again refers to the goal of modifying variable regions and/or constant regions or an antibody and further elaborates that the purpose of modifying variable regions is to change affinity or specificity. As has been discussed above, such a goal makes sense only in the context of altering a rearranged gene in an antibody producing cells, not un-rearranged genes of a transgenic mouse.

In light of the above remarks, it is believed that this rejection should be withdrawn.

Conclusion

It is believed that this document is fully responsive to the Office action dated 27 Feb 2006. In light of the above amendments and remarks, it is believed that the claims are now in

condition for allowance, and such action is respectfully urged.

Fees

Applicants contend that no fee is necessary in connection with the filing of this response. If a fee is determined to be due, authorization is hereby given to charge such a fee, to Deposit Account No. 18-0650.

Respectfully submitted,

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